CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-064

Correspondence

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 31, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: Please find attached the labeling edits in the PRECAUTIONS – General and CLINICAL TRIALS sections of the *DRAFT* labeling for NDA 21-064: DEFINITY™. Please submit to the Division A.S.A.P. on Tuesday, July 31, 2001, your letter of concurrence to the labeling. Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 31, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 19

COMMENTS: Please find attached the APPROVAL action letter and labeling to NDA 21-064: DEFINITY™ as of July 31, 2001. An official hard copy will be mailed to you. Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 30, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: **Please find attached minor revisions to the Phase 4 commitments in reference to NDA 21-064: DEFINITY™. Please submit to the Division by 5:30 p.m., July 30, 2001, your letter of concurrence to the Phase 4 commitments. Thank you.**

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 30, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 30

COMMENTS: Please find attached the *DRAFT ANNOTATED* labeling for NDA 21-064: DEFINITY™, as of 3:00 p.m., today, July 30, 2001. Also, attached is a "*clean*" DRAFT labeling, for ease of review. Please submit to the Division A.S.A.P. or by 5:00 p.m., July 30, 2001, your letter of concurrence to the labeling. * NOTE: The Division's NEW edits are bolded and highlighted in italics and deletions are in strike-outs. Thank you.

Document to be mailed: ☐ YES ☑ NO

28 pages redacted from this section of the approval package consisted of draft labeling

DuPont Pharmaceuticals Company

30 July 2001

DUPLICATE
N-000-BM

NDA ORIG AMENDMEN

Patricia Y. Love, M.D., Director
Medical Imaging & Radiopharmaceutical Drug Products
Document Control Room 18B-45 (HFD-160)
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #21-064
DEFINITY™ Vial for (Perflutren Lipid Microsphere) Injectable Suspension

Request for Additional Information

REF: RA/DEFI/54/01

Dear Dr. Love:

DuPont Pharmaceuticals Company (DuPont) is submitting this response to the Phase 4 Commitment comments received from the Agency via fax on 30 July 2001.

For ease of review, the questions/comments raised by the Agency are presented in **bold** text and followed by DuPont's response in plain text.

1) **Please find attached minor revisions to the Phase 4 commitments in reference to NDA #21-064: DEFINITY™. Please submit to the Division by 5:30 p.m., July 30, 2001, your letter of concurrence to the Phase 4 commitments. Thank you.**

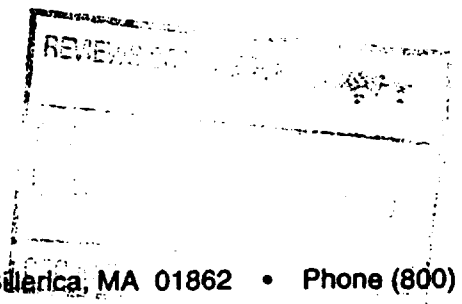
DuPont Pharmaceuticals agrees to the Phase IV commitments as outlined in the agency's fax of 30 July 2001.

If there are any questions regarding this submission, or you require further information to facilitate your review, please do not hesitate to contact me at (978) 671-8069.

Sincerely,

James M. Adie
Sr. Regulatory Affairs Associate

JMA/dmr



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 27, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 15	

COMMENTS: Please find attached the *DRAFT* labeling for NDA 21-064: DEFINITY™, as of 4:00 p.m., today, July 27, 2001. This *DRAFT* labeling is subject to change pending the review with the Office. Please submit to the Division by 10:00 a.m., Monday, July 30, 2001, your letter of concurrence to the labeling. * NOTE: The Division's NEW edit is in italics on page 6 and strike-out on page 12. Thank you.

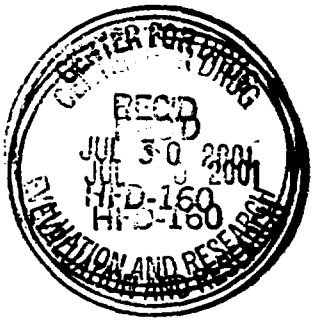
Document to be mailed: ☐ YES ☑ NO

14 pages redacted from this section of the approval package consisted of draft labeling

NDA ORIG AMENDMENT

DuPont Pharmaceuticals Company

DUPLICATE
N-000-Bm



27 July 2001

Patricia Y. Love, M.D., Director
Medical Imaging & Radiopharmaceutical Drug Products
Document Control Room 18B-45 (HFD-160)
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA ORIG AMENDMENT

RE: NDA #21-064
DEFINITY™ Vial for (Perflutren Lipid Microsphere) Injectable Suspension

Request for Additional Information

REF: RA/DEFI/51/01

Dear Dr. Love:

DuPont Pharmaceuticals Company (DuPont) is submitting this response to the Labeling comments received from the Agency via telephone and fax on 26 July 2001.

For ease of review, the questions/comments raised by the Agency are presented in **bold** text and followed by DuPont's response in plain text.

1) **As discussed at today's TCON, please find attached an additional Phase 4 commitment in reference to NDA #21-064: DEFINITY™. Please submitted to the Division by 11:00 a.m., Friday, July 27, 2001, your letter of concurrence to the Phase IV commitment. The Phase IV commitment is as follows:**

To perform a one-year adverse event surveillance study on patients receiving activated DEFINITY™ post launch of the product. The protocol will be submitted within 2 months of product launch and implemented with 4 months of design agreement. A final report will be submitted within 6 months of completion.

DuPont Pharmaceuticals Company (DPC) commits to performing a one-year adverse event surveillance study on patients receiving activated DEFINITY™. The protocols will be submitted within 2 months of product launch and implemented within 4 months of design agreement. A final report will be submitted within 6 months of study completion.

MEMO
INITIALS
DATE

2) **Please find attached the DRAFT labeling for NDA #21-064: DEFINITY™, as of 3:00 p.m. today, July 26, 2001. This DRAFT labeling is subject to change pending the review with the Office. Please submit to the Division by 11:00 a.m., Friday, July 27, 2001, your letter of concurrence to the labeling. *NOTE: The Division's new edits are in Italics on pages 8,9,11 (Table 3). Thank you.**

DuPont Pharmaceuticals Company (DPC) concurs with the agency's new edits on page 8 under the "Carcinogenesis, Mutagenesis, and Impairment of Fertility" section of the Package Insert. DPC assumes the correct wording in the first sentence should be "Impairment of male or female fertility was not observed..." and that "infertility" was a typographical error. DuPont also concurs with the agency's new edits on page 9 under the "Pregnancy Category B" section and with the addition of "activated" DEFINITY™ on page 11 in Table 3.

However, DuPont would like to provide additional rationale for the elimination of the word ' from the "Imaging" paragraph of the "DOSING AND ADMINISTRATION" section of the Package Insert. DuPont believes that the procedure for imaging under **DOSAGE AND ADMINISTRATION** should read, "Then inject activated DEFINITY™ (as described above) and begin imaging immediately." In response to the rationale presented in our 19 July 2001 letter, FDA indicated their concern that ultrasound contrast agents are the first class of drugs that are changed by the imaging device; and therefore, use of an imaging technique (i.e., harmonic imaging) that was different than that used in the pivotal trials (i.e., fundamental imaging) could represent a safety issue (e.g., could have different effect on the bubble characteristics such as stability). We would like to point out that the imaging techniques have identical effect on the bubble. The difference between and harmonic imaging does not arise from the use of different power delivered to the target (bubble and surrounding tissue) but rather results from **detection** of signal at different frequencies. In an ultrasound field, microbubbles resonate and can produce echoes not only at the transmit frequency but also at multiples of that frequency (harmonic frequencies). Thus, for example, a 2MHz-ultrasound probe at 0.8 mechanical index can detect a 2MHz signal imaging) or a 4MHz signal (harmonic imaging). In either case, the power that the beam delivers to the contrast agent is the same and harmonic imaging presents no unique safety issues.

DuPont would like to thank the Division for considering our request and DuPont is always available to discuss the agency's concerns in a teleconference if necessary.

If there are any questions regarding this submission, or you require further information to facilitate your review, please do not hesitate to contact me at (978) 671-8069.

Sincerely,

James M. Adie

James M. Adie
Sr. Regulatory Affairs Associate

JMA/dmr

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

JUL 27 2001

James M. Adie
Sr. Regulatory Affairs Associate
DuPont Pharmaceuticals Company
331 Treble Cove Road
North Billerica, MA 01862

RE: **NDA 21-064** Definity Vial for (Perflutren Lipid Microsphere) Injectable Suspension
MACMIS # 10199

Dear Mr. Adie:

This letter responds to DuPont Pharmaceuticals Company's (DuPont) request for comments, dated June 29, 2001, on proposed promotional materials for Definity. You submitted the following: a draft press release, a fact sheet, a Frequently Asked Questions and Answers sheet (Q&A), and draft labeling.

DDMAC, in consultation with the Division of Medical Imaging and Radiopharmaceutical Drug Products, has reviewed your proposed promotional materials and offers the following comments. Our comments on these proposed promotional materials should be applied to all current and future promotional materials for Definity with the same or similar claims and representations. Please note that our comments are based on draft labeling dated July 26, 2001, and are therefore subject to change in accordance with final approved product labeling.

Minimization of Risk Information

Your press release lacks fair balance and is misleading because it minimizes important risk information in the draft product labeling (PI) for Definity. The draft PI states that Definity is contraindicated for use in patients with cardiac shunts. However, your press release states that "caution should be exercised when Definity is administered to patients who may have cardiac shunts...." We recommend revising this risk information.

Your press release also minimizes important risk information because you have introduced the risk information with the header "Additional Background." We suggest revising the header to an introduction such as risk information or adverse events.

Misleading Claims

Promotional materials are misleading if they contain a representation or suggestion that a drug is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence. In your press release, you claim that "Definity may provide definitive diagnoses for millions of patients who are at a higher risk for developing coronary artery disease, including people who are overweight or who smoke...." Your claim regarding potential patients who are

at a higher risk of developing coronary artery disease including those who are overweight or who smoke is misleading because these patients were not specifically studied in your clinical trials. We recommend revising this claim.

In your press release, you present claims such as "ultrasound with Definity leads to better assessment of the heart's structure and function," "...increase the diagnostic reach of ultrasound," and "...reach confident diagnoses." These claims are misleading because they imply that the drug is more effective than has been demonstrated by substantial evidence. For example, Definity has not been shown to improve the measurement of ejection fraction or identify the type of wall motion abnormality over non-contrast echocardiograms.

In your press release, you also present the claim that "Definity produced more detailed images of the heart than echocardiography alone." This claim is misleading because it implies that the drug is more effective than has been demonstrated by substantial evidence. You fail to disclose that Definity produced more detailed images of the heart only in patients where echocardiography alone **was non-evaluable** (emphasis added).

You also claim that "... a diagnostic echocardiogram was achieved in three out of four patients." This claim is misleading because it implies that the "diagnostic echocardiogram" provided a correct diagnosis. We suggest revising your claim to a statement such as "an evaluable image" was achieved in 3 out of 4 patients.

Please note that our comments regarding the draft press release also apply to the Q&A sheet and the fact sheet. If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds DuPont that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 10199 and NDA 21-064.

Sincerely,

{See appended electronic signature page}

Warren Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 26, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 15	

COMMENTS: Please find attached the *DRAFT* labeling for NDA 21-064: DEFINITY™, as of 3:00 p.m., today, July 26, 2001. This *DRAFT* labeling is subject to change pending the review with the Office. Please submit to the Division by 11:00 a.m., Friday, July 26, 2001, your letter of concurrence to the labeling. * NOTE: The Division's NEW edits are in italics on pages 8, 9, and 11 (Table 3). Thank you.

Document to be mailed: ☐ YES ☑ NO

14 pages redacted from this section of the approval package consisted of draft labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 26, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: As discussed at today's TCON, please find attached an additional Phase 4 commitment, in reference to NDA 21-064: DEFINITY™. Please submit to the Division by 11:00 a.m., Friday, July 27, 2001, your letter of concurrence to the Phase IV commitment. Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 17, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897\436-7509	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 14

COMMENTS: **Please find attached the *DRAFT* labeling for NDA 21-064: DEFINITY™, as of 3:00 p.m., today, July 17, 2001. This *DRAFT* labeling is subject to change pending the review with the Office. Please submit to the Division by NOON, Monday, July 23, 2001, your letter of concurrence to the labeling. Thank you.**

Document to be mailed: ☐ YES ☑ NO

14 pages redacted from this section of the approval package consisted of draft labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 12, 2001

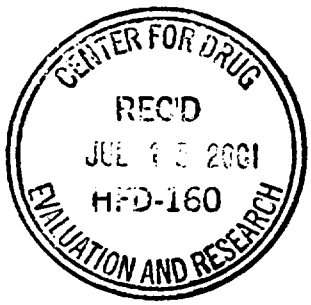
TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: **Please find attached additional Phase IV commitments, in reference to NDA 21-064: DEFINITY™. Please submit to the Division by NOON, Thursday, July 12, 2001, your letter of concurrence to the Phase IV commitments. Thank you.**

Document to be mailed: ☐ YES ☑ NO

DUPLICATE

DuPont Pharmaceuticals Company



12 July 2001

Patricia Y. Love, M.D., Director
Medical Imaging & Radiopharmaceutical Drug Products
Document Control Room 18B-45 (HFD-160)
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #21-064
DEFINITY™ Vial for (Perflutren Lipid Microsphere) Injectable Suspension

Request for Additional Information

REF: RA/DEFI/46/01

Dear Dr. Love:

DuPont Pharmaceuticals Company (DuPont) is submitting this response to the Pre-clinical/Clinical comments received from the Agency via telephone and fax on 12 July 2001.

For ease of review, the questions/comments raised by the Agency are presented in **bold** text and followed by DuPont's response in plain text.

Per our letter of January 22, 2001, and your submission of January 30, 2001, we remind you of the following Phase IV commitments (items 1 and 2 below):

1) **The completion of pre-clinical studies of the effects of mechanical ventilation on the microbubble characteristics and the toxicity of DEFINITY™. The protocols will be submitted with 6 months of the action letter and implemented within 6 months of design agreement.**

DuPont Pharmaceuticals Company (DPC) commits to perform pre-clinical studies of the effects of mechanical ventilation on the microbubble characteristics and the toxicity of DEFINITY™. The protocols will be submitted within 6 months of the action letter and implemented within 6 months of design agreement.

2) **Pending the results of the pre-clinical evaluation, the completion of mechanical ventilation on DEFINITY™ efficacy and safety profile in adults. The protocols will be submitted within 6 months of the completion of the studies in item 1 (above), and implemented within 6 months of study design agreement.**

DuPont Pharmaceuticals Company (DPC) commits to performing mechanical ventilation studies on DEFINITY™ efficacy and safety profile in adults pending the results of the pre-clinical studies in item 1 (above). The protocols will be submitted within 6 months of the completion of the pre-clinical studies, and implemented within 6 months of design agreement.

3) **In addition, we are requesting that you submit a Proposed Pediatric Study Request (PPSR) and your pediatric plan for addressing pediatric requirements under 21 CFR 314.55, within 120 days of the action letter.**

DuPont Pharmaceuticals Company (DPC) commits to submitting a Proposed Pediatric Study Request and a pediatric plan within 120 days of the action letter.

If there are any questions regarding this submission, or you require further information to facilitate your review, please do not hesitate to contact me at (978) 671-8069.

Sincerely,

James M. Adie

James M. Adie
Sr. Regulatory Affairs Associate

JMA/dmr

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 10, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: **Please find attached Phase IV commitments, in reference to NDA 21-064: DEFINITY™. Please submit to the Division by NOON, Wednesday, July 11, 2001, your letter of concurrence to the Phase IV commitments. Thank you.**

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 9, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

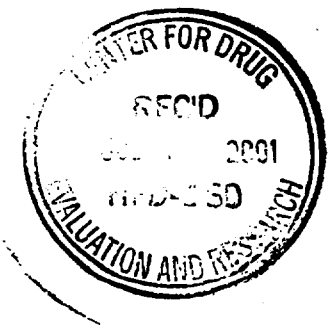
Total no. of pages including cover: 1

COMMENTS: In reference to NDA 21-064, and in accordance to 21 CFR Part 54, please provide financial disclosure information and forms for all investigators, primary investigators, and specifically for the blinded readers in the pivotal Phase 3 clinical trials by Tuesday, July 10, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

DUPLICATE

BM



DuPont Pharmaceuticals Company

10 July 2001

Patricia Y. Love, M.D., Director
Medical Imaging & Radiopharmaceutical Drug Products
Document Control Room 18B-45 (HFD-160)
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA #21-064
DEFINITY™ Vial for (Perflutren Lipid Microsphere) Injectable Suspension

Request for Additional Information

REF: RA/DEFI/43/01

Dear Dr. Love:

DuPont Pharmaceuticals Company (DuPont) is submitting this response to the Phase IV commitment request for pre-clinical studies received from the Agency via fax on 10 July 2001.

For ease of review, the questions/comments raised by the Agency are presented in **bold** text and followed by DuPont's response in plain text.

1) **It is known from clinical studies that contrast enhancement dissipates with time post dosing. Such dissipation, however, does not necessarily imply that the microspheres are no longer circulating in the body.**

In view of this proprietary information and the lack of pre-clinical and human pharmacokinetics data on the intact DEFINITY™ microspheres, we are requesting the following Phase IV commitment:

To perform pre-clinical study(ies) to determine the fate of the activated microspheres, characterizing the length of microsphere persistence and the potential for microsphere gas exchange. A draft protocol(s) should be submitted within 6 months post approval with initiation of the study(ies) within 6 months of agreement on protocol design. A final study report(s) should be submitted within one-year post study initiation.

DuPont Pharmaceuticals Company commits to performing a post approval pre-clinical study(ies) to determine the fate of the activated microspheres, characterizing the length of microsphere persistence and the potential for microsphere gas exchange. These studies will be aimed at supplementing our Phase I pharmacokinetic study DMP 115-905. This study was submitted with the original NDA and can be found in Volume 37, page 1. In this study we used Doppler ultrasound to demonstrate loss of DEFINITY™ microspheres and elimination of PFP in the blood.

If there are any questions regarding this submission, or you require further information to facilitate your review, please do not hesitate to contact me at (978) 671-8069.

Sincerely,

James M. Adie
Sr. Regulatory Affairs Associate

JMA/dmr

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 27, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: Please find attached the statistical comments in reference to NDA 21-064.

Please provide an official response to the NDA by noon, Friday, June 29, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

STATISTICAL COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Orig. Submission 01/30/01) **June 27, 2001**

EFFICACY ANALYSES REQUEST

1. In reference to submission dated 6/21/01, please provide a breakdown of your Table 2 by "abnormal" and "normal" patient populations. Also please provide an "N" for each reader.

2. Please provide an analysis for any 2 segments non-evaluable for wall motion at baseline that convert to evaluable and the correlation with MRI. Please also provide this by "normal" and "abnormal" patient populations.

3. Please provide an analysis of the correlation with MRI of increasing number of non-evaluable segments at baseline that converted post-Definity. You may consider doing this by grouping (for example 3-5 non-evaluable segments at baseline, 6-8 non-evaluable segments at baseline etc.).

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: June 26, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: Please find attached the clinical comments to NDA 21-064: DEFINITY. Please submit an official response to the NDA by noon, Thursday, June 28, 2001.

Thank you.

Document to be mailed: ☐ YES ☑ NO

ADVERSE EVENT TABLES SHOULD LIST THE NUMBER OF PATIENTS WITH EACH EVENT

SAMPLE TABLE NDA _____, DRUG X ANY AND ALL ADVERSE EVENTS IN ALL PATIENTS THAT RECEIVED ANY FORMULATION OR DOSE OF DRUG X				
	US	**EU**	**Japan**	**Totals**
N Patients Exposed	500	200	250	950
N (%) Patients with Any ADE	150 (30%)	x (%)	y (%)	z (%)
Body As a Whole N (%) patients with any	30 (6%)	etc	etc	
Fever	10 (2%)			
Headache	10 (2%)			
Pain	20 (4%)			
Etc.				
Cardiovascular Symptoms N (%) patient with any	10 (2%)			
Arrhythmia	7 (1%)			
Chest pain	5 (1%)			
Etc.				

This table should be accompanied with subgroup tables to display the data for different doses, formulations, sites with potentially different reporting or monitoring practices, genders, ages, body size or weight, etc. (as appropriate).

* INSERT ROW: TOTAL N (ADVERSE EVENTS)

Events > 0.5%

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2001

TO: MR. JAMES ADIE **Sr. Regulatory Affairs Associate**	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: Please find attached the chemistry comments to NDA 21-064: DEFINITY.

Please provide an official response to the NDA as soon as possible or by Tuesday, May 15, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

CHEMISTRY COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 01/30/01) **May 1, 2001**

1. The excipients glycerin and propylene glycol may at times be contaminated with [redacted] a known toxic substance. Provide additional specifications for acceptance testing for this contaminant for each batch of these two excipients received by DuPont. Also, provide appropriate validation data for the method(s) proposed.

APPEARS THIS WAY
ON ORIGINAL

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 7, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: **Please find attached pharmacology/toxicology comments to NDA 21-064: DEFINITY. Please provide an official response to the NDA as soon as possible or by Friday, May 11, 2001. Thank you.**

Document to be mailed: ☐ YES ☑ NO

PHARMACOLOGY/TOXICOLOGY COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 01/30/01) **May 7, 2001**

1. Definity seems to be affecting the QT_C interval in animals with moderate pulmonary hypertension. Specifically, after 200 μL, Definity appeared to significantly (the lower band of CI does not overlap) affect QT_C compared with control. However, the result section indicated that injection of Definity did not alter QT_C interval.

   Please provide an explanation of how this conclusion was reached.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 9, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 1

COMMENTS: In reference to NDA 21-064, please provide a hard copy and a diskette of the latest DEFINITY draft vial (container) and carton labels as soon as possible or by Tuesday, May 15, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 16, 2001

TO: MR. JAMES ADIE Sr. Regulatory Affairs Associate	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8069	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 1

COMMENTS: From the telephone conversation this morning, in reference to NDA 21-064, please provide on diskette ( ) and hard copy of the updated DEFINITY draft package insert with the correct format and pagination, as soon as possible or by Friday, May 18, 2001. If there is a delay, please let me know. . Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2001

TO: MS: MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: **Please find attached the chemistry comments to NDA 21-064: DEFINITY.**

Please provide an official response to the NDA as soon as possible or by May 3, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

CHEMISTRY COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 01/30/01) **April 26, 2001**

1. Please provide (4) copies of the updated method validation packages – all the method numbers should be proper and corresponding to the numbers in the specifications.

2. [redacted]

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 26, 2001

TO: MS: MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	

Total no. of pages including cover: 1

COMMENTS: **In reference to NDA 21-064, please submit a hard copy and a diskette of the latest Definity draft package insert as soon as possible or by May 3, 2001. Thank you.**

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 23, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: **Please find attached the statistical comments to NDA 21-064: Definity.**

Please provide an official response to the NDA Monday, April 30, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 12, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: **Please find attached the clinical and statistical comments to NDA 21-064: DEFINITY. Please provide an official response to the NDA as soon as possible or by Monday, April 16, 2001. Thank you.**

Document to be mailed: ☐ YES ☑ NO

CLINICAL AND STATISTICAL TO THE SPONSOR

NDA 21-064 (Dates of Submission 01/30/01 and 03/26/01) **April 12, 2001**

1. Please refer to your submission dated – 03/26/01, Page 3 of 3, Table 2: Please provide a subset analysis of the normal and abnormal.

2. In reference to the training method, is the reader identifying the outline blood pool containing Definity or the edges of the myocardium containing Definity to determine Left Endocardial Border (LVEB) delineation?

3. Please provide a copy of the Definity approved Canadian package insert that goes along with the vial.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 10, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Co.	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (973) 671-8772	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: Please find attached the chemistry comments to NDA 21-064. Please provide an official response to the NDA as soon as possible. Thank you.

Document to be mailed: NO

CHEMISTRY COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 04/04/01) **April 10, 2001**

1. Please provide on diskette in [redacted] the current carton and vial labels for DEFINITY.

APPEARS THIS WAY
ON ORIGINAL

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 11, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: Please find attached the pharmacology/toxicology comments to NDA 21-064: DEFINITY. Please provide a response as soon as possible or by Wednesday, April 18, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

PHARMACOLOGY/TOXICOLOGY COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 01/31/01) **April 11, 2001**

1. For DRR 2001-01: Please indicate the formula used for the QT correction. What are the rationale for the adoption of this formula?

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: April 10, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Co.	Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (973) 671-8772	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: Please find attached the chemistry comments to NDA 21-064. Please provide an official response to the NDA as soon as possible. Thank you.

Document to be mailed: NO

CHEMISTRY COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 04/04/01) **April 10, 2001**

1. Please provide on diskette in format the current carton and vial labels for DEFINITY.

APPEARS THIS WAY
ON ORIGINAL

DuPont Pharmaceuticals Company

3 April 2001

Patricia Y. Love, M.D., Director
Medical Imaging & Radiopharmaceutical Drug Products
Document Control Room 18B-45 (HFD-160)
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DUPLICATE

N-000 BM

ORIG AMENDMENT

RE: NDA #21-064
DEFINITY™ (Perflutren Lipid Microsphere) Injectable Suspension

REF: RA/DEFI/11/01

Dear Dr. Love:

On 22 January 2001, FDA notified DuPont Pharmaceuticals Company (DuPont) that DuPont's request for the deferral of pediatric studies with DEFINITY™ (Perflutren Lipid Microsphere) Injectable Suspension was acceptable under 21 CFR 314.55(b). In this letter, FDA also requested DuPont to commit to several preclinical and clinical studies in our upcoming response to the 4 August 2000 approvable letter. FDA recommended that these studies take a stepwise approach to assess pediatric safety in an attempt to preclude potential unforeseen events that might arise with the use of a microbubble contrast agent early in life. DuPont did submit an Amendment to our pending NDA #21-064 on 31 January 2001, which included commitments to conduct the requested preclinical and pediatric studies and an additional Phase IV adult study. Please note that DuPont intends to use these data to seek pediatric exclusivity under Section 505A of the Food, Drug, and Cosmetic Act.

DuPont is now in the process of designing the stepwise development plan for the pediatric and Phase IV studies suggested by FDA. DuPont has developed a plan to address FDA's request that we believe is appropriate in terms of timing and order. DuPont requests that the Agency review the proposed development program and comment on the timing and order of these studies. DuPont would also appreciate FDA's comments on DuPont's questions presented below.

1. FDA has requested that protocols for studies in pediatrics >2 years of age and studies in infants be submitted within 6 months of 22 January letter. FDA then requests that the >2 years of age study be complete before initiating studies in infants. Does FDA want to see draft protocols for infants by 22 July or is it more appropriate to provide protocols that incorporate the results from the >2 years of age pediatric studies at a later date?

2. FDA has requested that DuPont perform a preclinical study using an immature lung animal model. DuPont requests that FDA provide its rationale for requesting this study. Normal, full term neonates have fully formed pulmonary vasculature and airways suggesting that such a study may not be necessary or appropriate. Moreover, DuPont does not envision the use of DEFINITY™ in premature/preterm neonates.

3. If FDA does determine that an immature lung animal study is still required, DuPont requests that FDA provide guidance on an appropriate animal model to conduct such a study.

4. Please find below, for your review and comment, a draft development plan including proposed timing, which DuPont believes will address FDA's concerns and requests as contained in the 22 January 2001 letter. Is this plan acceptable to FDA?

Step One:

- Studies in **Pediatric Patients >2 years of age**. Protocol to be submitted by 22 July 2001 (6 months of receipt of 22 January letter).

- **Preclinical studies** of the effects of mechanical ventilation on microbubble characteristics and toxicity. Protocol to be submitted by 22 July 2001 (6 months of receipt of 22 January letter).

- If required, **Preclinical studies** of DEFINITY™ in Immature Lung Animal model, to include evaluation of effects of mechanical ventilation and gas exchange. Protocol to be submitted by 22 October 2001 (9 months of receipt of 22 January letter).

Step Two:

- Pending the results from the preclinical mechanical ventilation studies described above, mechanical ventilation studies of DEFINITY™ efficacy and safety in **Adults**. Protocol to be submitted within 6 months of completion of preclinical mechanical ventilation studies.

Step Three:

- Studies in **Infants**. Protocol to be submitted within 6 months of completion of patients >2 years. Based on results in older pediatric patients, the design or dosing in infants may need to be modified.

- Studies in **Neonates**. Protocol to be submitted within 6 months of completion of infants.

DuPont believes that the plan outlined above represents a reasonable approach to the studies requested by FDA. DuPont would appreciate FDA's position on the above items at your earliest convenience so that DuPont can continue to move forward with our development plans.

If you have any questions or need additional information, please feel free to contact me directly at (978) 671-8495 or Mary Matthew at (978) 671-8772.

Sincerely,

Robert A. Morgan
Sr. Director, Regulatory Affairs

RAM/dmr

FACSIMILE TRANSMISSION RECORD

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Medical Imaging and
Radiopharmaceutical Drug Products (HFD-160)
Parklawn Building, Room 18B-06
5600 Fishers Lane, Rockville, Maryland 20857

2 Number of Pages (including cover sheet) **Date: March 21, 2001**

TO: **MS. MARY MATTHEW**
DuPont Pharmaceuticals Company

Fax Number: (978) 663-6897 **Voice Number: (978) 671-8772**

From: Thuy Nguyen
Regulatory Health Project Manager

Fax Number: (301) 480-6036 **Voice Number: (301) 827-7510**

MESSAGE:

Please find attached the statistical information request letter in reference to NDA 21-064: DEFINITY. Please provide an official response to the NDA by March 28, 2001. Thank you.

Please note that we do not consider this a formal communication.
NOTE: If you do not receive a legible document, or do not receive all of the pages, please telephone us immediately at the voice number above.
THIS DOCUMENT IS INTENDED FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

CC: Original NDA 21-064
HFD-160/Div. File
HFD-160/Nguyen

[* See STATS IR Letter in Letter folder.]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-064

INFORMATION REQUEST LETTER

MAR 21 2001

DuPont Pharmaceuticals Company
Attention: Ms. Mary A. Matthew
331 Treble Cove Road, Building 600-1
North Billerica, MA 01862

Dear Ms. Matthew:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DEFINITY™ [Vial for (Perflutren Lipid Microsphere) Injectable Suspension] - submission dated January 30, 2001.

We are reviewing the statistical section of your submission and have the following comments and information requests:

1) Please provide the listings of patients who were normal/abnormal (based on MRI wall motion) at baseline and their wall motion evaluation post-DMP for both studies -006 and -007.

2) Please provide the listings of non-evaluable (at >2 adjacent segments) patients at baseline who became evaluable at post for both studies -006 and -007.

We need your prompt written response by March 28, 2001, to continue our evaluation of your NDA.

If you have any questions, call Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Mahboob Sobhan, Ph.D.
Statistical Reviewer
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 8, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510

Subject: NDA 21-064: DEFINITY

Total no. of pages including cover: 2

COMMENTS: Please find attached the pharmacology/toxicology comments in reference to NDA 21-064: DEFINITY. Please provide an official response to the NDA as soon as possible or by Wednesday, March 14, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

PHARMACOLOGY/TOXICOLOGY COMMENTS TO THE SPONSOR

21-064 (Date of Submission 01/30/01) **March 8, 2001**

1. Please provide a copy of the ***unedited*** video of the microcirculation study as supplied by Dr. Jonathan Linde, M.D.

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 5, 2001

TO: MS. MARY MATTHEW	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 3	

COMMENTS: Please find attached the chemistry comments to NDA 21-064: **DEFINITY.** Please submit an official response to the NDA as soon as possible. Thank you.

Document to be mailed: ☐ YES ☑ NO

2 pages redacted from this section of the approval package consisted of draft labeling

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: February 27, 2001

TO: Ms. Mary Matthew	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: DuPont Pharmaceuticals Company	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (978) 663-6897	**Fax number:** (301) 480-6036
Phone number: (978) 671-8772	**Phone number:** (301) 827-7510
Subject: NDA 21-064: DEFINITY	
Total no. of pages including cover: 2	

COMMENTS: Please find attached the clinical comments to NDA 21-064: DEFINITY. Please submit an official response to the NDA A.S.A.P. or by March 6, 2001. Thank you.

Document to be mailed: ☐ YES ☑ NO

CLINICAL COMMENTS TO THE SPONSOR

NDA 21-064 (Date of Submission 01/30/01) **February 27, 2001**

1. As requested on page 5, item #5, of the Approvable Letter of August 4, 2000, please submit case report forms (CRFs) for each patient who died during a clinical study or who did not complete a study because of an adverse event.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-064

JAN 22 2001

Dupont Pharmaceuticals Company
Attention: Robert Morgan, Regulatory Affairs
331 Treble Cove Road, Bldg. 600-1
North Billerica, MA 01862

Dear Mr. Morgan:

Reference is made to your correspondence dated November 21, 2000, requesting a deferral under 21 CFR 314.55(b) and 601.27(b) and a partial waiver under 21 CFR 314.55(c)(3) and 601.27(c)(3) for pediatric studies.

We have reviewed the information you have submitted and agree that deferral of pediatric studies and the performance of them post approval is acceptable under 21 CFR 314.55(b) and 601.27(b).

However, we cannot grant a partial waiver for pediatric studies in neonates based on your submission under 21 CFR 314.55(c)(3) and 601.27(c)(3). Instead, we are granting a deferral for neonatal studies.

In regard to neonatal studies, it may be prudent to design and perform such studies after evaluating the outcome of pediatric trials in older pediatric age groups. Unforeseen safety concerns may arise in the other age groups of the pediatric population, or the present safety concerns may exacerbate. Such a stepwise approach to the question of pediatric safety may preclude potential unforeseen surprises that might arise with the use of a bubble agent early in life.

Under the Pediatric Rule, applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration must contain a pediatric assessment unless the Sponsor has obtained a waiver or deferral of pediatric studies [21 CFR 314.55 (a) and 601.27 (a)]. Although we have granted you a deferral of pediatric studies, in order to qualify for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act (as established under section 111 of Title 1 of the Food and Drug Administration Modernization Act of 1997), we recommend you address the following preliminary comments:

1. For studies in infants and patients > 2 years, protocols should be submitted within 6 months of this letter, and the protocols should be implemented within 6 months of FDA agreement on the protocol designs. Before initiating the studies in infants, complete and evaluate the results in pediatric patients > 2 years. Based upon the results in older pediatric patients, the design or dosing in infants may need to be modified.

2. Before the neonatal studies can be appropriately designed, data are needed from dosing studies in infants, and studies in immature lung animal models. These should consider the effects of mechanical ventilation and gas exchange in the bubble. Protocols for these preliminary studies should be submitted within 9 months of this letter and implemented within 6 months of design agreement. The protocols for the neonatal studies should be submitted 6 months after completion of the preliminary studies. The neonatal protocols should be implemented within 6 months of FDA agreement on their designs.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. If you are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Additionally, since the mechanical ventilation effects can be important in adults and pediatric patients these studies per se may be considered as separate phase 4 requirements (i.e., not part of the pediatric plan). Therefore, in your resubmission please commit to the following:

a. The completion of preclinical studies of the effects of mechanical ventilation on the microbubble characteristics and the toxicity of Definity. The protocols will be submitted within 6 months of this letter and implemented within 6 months of design agreement.

b. Pending the results of the preclinical evaluation, the completion of mechanical ventilation on Definity's efficacy and safety profile in adults. The protocols will be submitted within 6 months of the completion of the studies in item a., and implemented within 6 months of design agreement.

We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have questions, please contact Thuy M. Nguyen, Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

/S/

Patricia Y. Love, M.D., M.B.A.
Director, Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DuPont Pharmaceuticals Company

21 November 2000

Patricia Y. Love, M.D.
Medical Imaging & Radiopharmaceutical Drug Products
Document Control Room 18B-45 (HFD-160)
Office of Drug Evaluation III
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG

RE: NDA #21-064
DEFINITY™
Vial for (Perflutren Lipid Microsphere)
Injectable Suspension

Notification of Intent to Amend NDA
Request for Deferral of Pediatric Studies

REF: RA/DEFI/55/00

Dear Dr. Love:

On behalf of the DuPont Pharmaceuticals Company (DuPont), I am writing to notify you of DuPont's intent to amend NDA No. 21-064 for DEFINITY™ [Vial for (Perflutren Lipid Microsphere) Injectable Suspension] as required under 21 CFR 314.110. The target is to have all of the necessary information addressing the questions and concerns raised by the Agency in the 4 August 2000 approvable letter ready for submission by the end of December 2000.

Also by way of this letter, DuPont is requesting a deferral and a partial waiver of the pediatric clinical studies required after 2 December 2000. DuPont's proposed clinical plan and partial waiver request are contained in Appendix A.

The FDA has defined four (4) pediatric age ranges: (1) neonates (birth to 1 month), (2) infants (1 month to 2 years), (3) children (2 years to 12 years), and (4) adolescents (12 years to 16 years). In discussions with Pediatric Cardiologists, pediatric patients from the categories of infants, children, and adolescents would be suitable for study with DEFINITY™. This proposed plan does not include neonates. The primary goal of this single pediatric study will be to assess

safety and provide dosing recommendations for DEFINITY™ to pediatric echocardiographers. DEFINITY™ will be administered in fixed dose increments based on patient weight. Dose escalation will be performed within each subject until optimal left ventricular opacification is attained. Efficacy will be limited to institutional evaluations of left ventricular cavity opacification and endocardial border delineation versus baseline imaging. Inclusion criteria will include referral for echocardiographic functional assessment and sub-optimal baseline imaging. The age range will be from one month to 16 years of age. DuPont requests that this proposed pediatric study be deferred to a Phase IV commitment. DuPont commits to submit a proposed protocol to FDA within 6 months post approval. DuPont further commits to initiate the clinical study within six months after receiving FDA's agreement on the study design.

DuPont also requests that a partial waiver be given for neonates. The use of DEFINITY™ in neonates would not be beneficial nor do we believe that any physician is likely to administer the product in this age group based on discussions with pediatric cardiologists. Therefore, under the requirements for granting a waiver, i.e., showing that DEFINITY™ does not represent a meaningful therapeutic benefit and that DEFINITY™ is not likely to be used in a substantial number of patients, we believe that a partial waiver for this age group is appropriate.

It is DuPont's hope that we can come to agreement with the Agency by the end of this year on our request for a partial waiver (excluding neonates) and the deferral to Phase IV for pediatric studies using DEFINITY™ for echocardiography imaging. We do recognize that the FDA has up to 60 days to review our proposal, but we are confident that we can continue to work with the Agency to expedite this review process.

Thank you for your consideration of our requests. If you have any questions or would like to discuss our proposals in more detail, please contact me directly at (978) 671-8495. I look forward to hearing from you in the very near future.

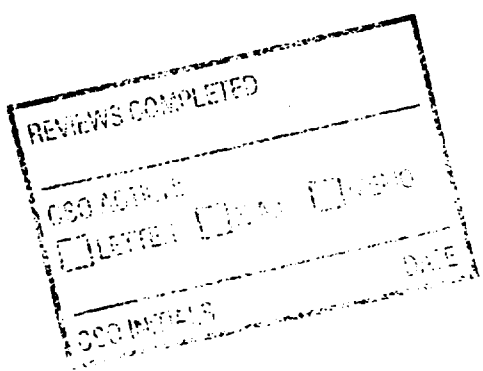
Sincerely,

Robert A. Morgan
Sr. Director, Regulatory Affairs

RAM/dmr

cc: Dr. Victor Raczkowski, FDA ODE III
Thuy Nguyen, Project Management, FDA

Enclosure



APPENDIX A

Proposal to request deferral of pediatric studies until after DEFINITY™ approval

DEFINITY™ is indicated for left ventricular opacification and improvement of endocardial border delineation in patients with suboptimal echocardiograms. Clinical trials with DEFINITY™ in adult patients demonstrated that it is safe and effective for this application.

The assessment of cardiac function in adult patients using echocardiography is often hampered by a patient's body habitus or other factors such as obstructive lung disease. The need to improve the quality of endocardial border delineation in the pediatric population is limited. In general, due to the smaller dimensions of the chest cavity in pediatric patients, higher frequency transducers can be effectively utilized. Higher frequency transducers permit improved spatial resolution and better appreciation of endocardial borders.

Only in relatively rare instances (e.g., Kawaski Disease) is coronary artery disease detected in the pediatric population.

In the United States in 1999, the number of trans-thoracic echocardiography procedures performed in patients under the age of 18 was 536,980[1]. Most of these procedures are performed to assess valvular disorders, such as mitral valve prolapse, or to assess atrial or ventricular septal defects. It is estimated that less than 10% of these total cases would be for functional evaluation and only a small subset of these patients undergoing functional assessment would present with suboptimal echocardiograms and be candidates for echo enhancement. The total population of pediatric patients eligible for echo contrast is less than the limit of 50,000 that FDA has chosen as the cut-off for a substantial number of pediatric patients.

The FDA has defined four (4) pediatric age ranges: (1) neonates (birth to 1 month), (2) infants (1 month to 2 years), (3) children (2 years to 12 years), and (4) adolescents (12 years to 16 years). In discussions with Pediatric Cardiologists, pediatric patients from the categories of infants, children, and adolescents would be suitable for study with DEFINITY™. The use of DEFINITY™ in neonates would not be beneficial nor would any physician likely administer the product in this age group. Therefore, DuPont Pharmaceuticals requests a waiver for neonates.

Pediatric patients with Kawasaki disease, heart transplant recipients, patients with transposition of the great vessels, or patients who have undergone previous cardiac surgery would most likely be the patients referred for functional echocardiographic assessment. Those who have poor or suboptimal baseline echo studies may be possible candidates for echo contrast enhancement.

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[1] AMR (Arlington Medical Resources, Inc.) Echocardiography Market Guide, United States Edition, 2000.

In an effort to provide dosing information to physicians who believe the potential benefit of DEFINITY™ outweighs the potential risks in this patient population, the sponsor is proposing the following post approval phase IV study:

A Phase IV study to assess the Safety and Efficacy of DEFINITY™ in the pediatric population

The primary goal of this pediatric study will be to assess safety and provide dosing recommendations for DEFINITY™ to pediatric echocardiographers. DEFINITY™ will be administered in fixed dose increments based on patient weight. Dose escalation will be performed within each subject until optimal left ventricular opacification is attained. Efficacy will be limited to institutional evaluations of left ventricular cavity opacification and endocardial border delineation versus baseline imaging. Inclusion criteria will include referral for echocardiographic functional assessment and sub-optimal baseline imaging. The age range will be from one month to 16 years of age. Patients will be stratified by age to one of three groups: infants, children, and adolescents. Twelve to sixteen subjects will be enrolled in each treatment group. This study will be a sequential cohort study in that enrollment will be done by descending age group.

Monitoring of vital signs, 12-lead ECG's, oxygen saturation, continuous single lead ECG monitoring, clinical chemistry, hematology, and adverse events will assess safety. Patients will be monitored post dosing for up to 72 hours.

DuPont commits to submit a proposed protocol to FDA within 6 months post approval. DuPont further commits to initiate the clinical study within 6 months after receiving FDA's agreement on the study design. Due to the limited patient population, we anticipate that it will take up to one year for enrollment, especially in the younger age groups.

14 pages redacted from this section of the approval package consisted of draft labeling